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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,825	03/22/2001	Keith D. Allen	R-849	6413

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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,825	ALLEN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

od for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

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)☒ Responsive to communication(s) filed on *07 October 2004*.
)☐ This action is **FINAL**. 2b)☒ This action is non-final.
)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

osition of Claims

)☒ Claim(s) *1-5,8-11,17-23,27-31,33,35,42,45 and 47* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) *1-5, 8-11, 17-23, 27-31, 33, 35, 42, 45 and 47* is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction and/or election requirement.

cation Papers

☐ The specification is objected to by the Examiner.
☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

y under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

ent(s)

otice of References Cited (PTO-892)
otice of Draftsperson's Patent Drawing Review (PTO-948)
formation Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
aper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is a reply to the Paper filed 7 October 2004 in reply to the Non-Final Office Action mailed 4 May 2004. Claims 1-5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 were considered in the 4 May Office Action. Claims 1, 3, 10, 23 and 27 were amended and claims 12 and 32 were canceled in the 7 October Paper. Claims 1-5, 8-11, 17-23, 27-31, 33, 35, 42, 45 and 47 are presently pending and under consideration.

Response to Amendment

Claim Rejections - 35 USC § 112

Rejection of claims 10 and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claims 1 and 3 are rejected under 35 U.S.C. 102(b) as being anticipated by Qin *et al.* (1992) *J. Biol. Chem.* 267:8458-8463 is withdrawn.

New Grounds

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 42, 45 and 47 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. §112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001

The Examiner is using the following definitions in evaluating the claims for utility.

"Specific"-A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial"-A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible"- Credibility is assessed for the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established"-a specific, substantial and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material alone or taken with the knowledge of one skilled in the art.

The rejected claims are directed to a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene wherein the mouse exhibits a phenotype comprising a hyperactive behavior and methods of using said mouse. The specification teaches a mouse comprising a knockout of the cGMP phosphodiesterase gene comprising SEQ ID NO: 19 and states, "[h]omozygous mice exhibited increased activity, traveling a much greater total distance and exploring the open field more in the open field test. This observation indicated hyperactivity in the homozygous state" (page 61).

The specification asserts that the claimed mouse is useful as a model of disease and provides a unique animal model for testing and developing new treatments relating to the phenotype. The specification also provides generic teaching regarding screening for compounds capable of ameliorating disease symptoms (see especially the discussion beginning in the second full paragraph on page 24 and continuing through the first full paragraph on page 32).

The utilities for the claimed mouse asserted in the specification are not substantial. First, there is nothing of record that would lead one to believe that a mouse that "[travels] a greater total distance and [explores] the open field more in an open field test" is a model of pathological hyperactivity or can be used to identify drugs that ameliorate pathological hyperactivity. For example, the mouse might be motivated to travel greater distances because of the visual problems also exhibited by the mouse (*i.e.*, the mouse must be closer to an object to identify it). Alternatively, the mouse might simply be more curious and, therefore, more inclined to explore its environment.

Furthermore, even if one were to assume, *arguendo*, that the behavior exhibited by the mouse evidenced hyperactivity in the mouse, there is nothing in the art or present disclosure to suggest that the hyperactivity exhibited by the mouse is relevant to the pathological state in humans or other animals. Neither the art nor the instant disclosure establishes a link between cGMP phosphodiesterase alpha and conditions such as ADHD in humans. One cannot assume that a mouse comprising a disrupted allele and a given phenotype is immediately useful as a model of a disease having some similar phenotypic features. Olsen *et al.* GABA in the Nervous System (2000), 81-96. Editor(s): Martin, David L.; Olsen, Richard W. Lippincott Williams & Wilkins: Philadelphia, PA teaches, "although gene targeting is often useful in delineating the

contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products." (page 82, column 1, emphasis added). Thus, Olsen states what is well-known in the art, which is that the phenotype displayed by a knockout mouse is a conglomeration comprised of phenotypic characteristics that are a direct result of the ablated gene being absent, cGMP phosphodiesterase alpha in the instant case, and phenotypic characteristics that are the outward manifestation of a myriad of compensatory responses to the absence of the ablated gene. The present application describes only a set of phenotypic characteristics with no disclosure of how these characteristics are related to the ablated allele, let alone how they are related to disease states in humans that do not involve disruption of the cGMP phosphodiesterase alpha subunit. In that regard, it is noted that although a number of human patients comprising homozygous disruptions of the rod cGMP phosphodiesterase alpha subunit have been identified (see, *e.g.*, Dryja *et al.* (1999) *Invest. Ophthalmol. Vis. Sci.* 40:1859-1865), the Examiner is unaware of any evidence of related hyperactivity in these patients. Thus, the relationship of the relative propensity of the claimed mice to travel a much greater total distance and explore the open field more in the open field test to any pathological state in humans remains to be established.

In view of these considerations, the skilled artisan clearly would not be able to use the claimed mouse as asserted without considerable experimentation to reasonably confirm that the mouse could be used as a model to develop therapeutic agents for the treatment of hyperactivity

as suggested. Therefore, neither the application nor the art adequately discloses a substantial utility for the claimed invention.

Applicant should explicitly identify a specific and substantial credible utility for the claimed invention and establish a probative relation between any evidence of record and the originally disclosed properties of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42, 45 and 47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-5, 8-11, 17-23, 27-31, 33 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene comprising SEQ ID NO: 19, wherein the mouse lacks production of a functional cGMP phosphodiesterase alpha subunit gene and exhibits an eye abnormality consistent with retinitis pigmentosa, and a targeting construct comprising SEQ ID NO: 19, does not reasonably provide enablement for a transgenic

mouse comprising a homozygous disruption of any cGMP phosphodiesterase alpha subunit gene, a mouse that does not comprise an eye abnormality consistent with retinitis pigmentosa or a targeting construct that does not comprise SEQ ID NO:19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: Claims are directed to a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein said mouse lacks production of functional cGMP phosphodiesterase alpha subunit protein and exhibits a phenotype comprising an eye abnormality or hyperactive behavior. Claims are also directed to a targeting construct comprising a polynucleotide sequence homologous to a cGMP phosphodiesterase alpha subunit gene, methods of making and using the claimed mouse and an embryonic stem cell having the disruption useful for making the mouse.

On page 5, the specification defines a “gene” as including “any DNA sequence that hybridizes to the complement of the coding sequence disclosed herein”. Thus, given its broadest

reasonable interpretation, the cGMP phosphodiesterase gene of the claims encompasses any gene comprising a DNA sequence that hybridizes to the cGMP phosphodiesterase sequence disclosed in the application, which includes genes having limited homology to the disclosed gene. Thus, the claims encompass targeting vectors comprising broadly divergent genes, mice and cells comprising disruption of broadly divergent genes wherein the mouse might exhibit any eye abnormality or need not exhibit an eye abnormality, and methods of making and using these broadly divergent products. Therefore, as the enablement provided must reasonably correlate with the scope of the protection sought, the disclosure must teach the skilled artisan how to make and use the broadly divergent subject matter within the scope of the claims.

State of the prior art and level of predictability in the art: The art teaches that, within mice, the phenotype arising from insertion or deletion of even a well-characterized gene is unpredictable. Doetchman (1999) *Lab. Animal Sci.* 49:137-143 (already of record) teaches, "[o]ne often hears the comment that genetically engineered mice…are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype. These expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies" (page 137, paragraph 1). Doetchman goes on to teach, "it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies" (page 140, column 2, third full paragraph) and "[a]pparent lack of phenotype more likely reflects or inability to ask the right questions, or our lack of tools to answer them" page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation of a transgenic mouse is highly unpredictable.

Dryja *et al.* (*supra*) teaches that mutations in the gene encoding the α subunit of the rod cGMP-phosphodiesterase is associated with autosomal recessive retinitis pigmentosa in humans. However, the art is silent with regard to the phenotypic characteristics associated with disruption of any cGMP phosphodiesterase gene that hybridizes with the sequence disclosed in the instant application.

Amount of direction provided by the inventor and existence of working examples: The specification teaches a mouse comprising a knockout of the cGMP phosphodiesterase gene comprising SEQ ID NO: 19 and phenotypic characteristics of the homozygous mouse such as eye abnormalities characteristic or retinitis pigmentosa and increased activity in the open field test.

However, the specification provides no guidance as to which genes, other than the cGMP phosphodiesterase alpha subunit gene comprising SEQ ID NO: 19, should be disrupted to provide the phenotypes recited in the claims and does not teach the skilled artisan how to use a mouse exhibiting a phenotype that does not comprise the eye abnormalities characteristic of retinitis pigmentosa. Although, as discussed above, the specification asserts that the claimed mouse is useful as a model of disease and provides a unique animal model for testing and developing new treatments relating to the phenotype and provides generic teachings regarding screening for compounds capable of ameliorating disease symptoms. The specification fails to disclose how the phenotypic characteristics of the mouse, other than those consistent with retinitis pigmentosa, are correlated with a pathological state such that the skilled artisan would be able to use the mouse to develop treatments relating to those phenotypes.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to make or use the full scope of the claimed invention without having to engage in undue experimentation. First, although the claims broadly encompass targeting constructs comprising the nucleic acid sequence of any gene that hybridizes with the disclosed nucleic acid under unspecified conditions, the disclosure only teaches how to use a mouse made using a targeting vector comprising SEQ ID NO: 19. Therefore, the skilled artisan would have to experiment to determine how to use a mouse made with the many broadly divergent targeting vectors encompassed by the claims that do not comprise SEQ ID NO: 19.

Furthermore, although the claims embrace a mouse comprising a disruption of any gene that meets the broad definition of a cGMP phosphodiesterase alpha subunit gene provided in the specification, wherein the mouse exhibits a phenotype comprising an eye abnormality or hyperactive behavior, the specification does not disclose which genes within this definition can be disrupted to provide the phenotypes recited in the claims. Therefore, the skilled artisan would have to resort to empirical experimentation, disrupting each gene comprising sequence that hybridizes with the disclosed nucleic acid to determine which disruptions result in the recited phenotype. Therefore, making the full scope of the claimed invention would require undue experimentation.

Finally, because neither the art nor the instant disclosure teach the skilled artisan how embodiments falling within the broad scope of an eye abnormality, other than those that are consistent with retinitis pigmentosa, can be used as a model of disease, one of ordinary skill would have to experiment to establish which eye abnormalities can be reasonably correlated with

a disease state such that the mouse can be used to identify a compound useful in the treatment of disease.

In view of these considerations, making and using the claimed invention beyond the scope indicated as being enabled herein above would clearly require undue experimentation. Therefore, the claims are properly rejected as failing to meet the enablement requirement of 35 USC §112, first paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Note: The following rejection applies to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention and does not evidence a patentable utility for the invention. MPEP 2122 states: "In order to constitute anticipatory prior art, a reference must identically disclose the claimed compound, but *no utility need be disclosed by the reference*. *In re Schoenwald*, 964 F.2d 1122, 22 USPQ2d 1671 (Fed. Cir. 1992)" (emphasis added).

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Qin *et al.* (1992) *J. Biol. Chem.* 267:8458-8463 (previously made of record) in view of Tsang *et al.* (1996) *Science* 272:1026-1029 and Dryja *et al.* (*supra*).

Claim 1 directed to a targeting construct comprising a first and second polynucleotide sequence homologous to a cGMP phosphodiesterase alpha subunit gene and a selectable marker gene located between the first and second polynucleotide sequences, claim 2 limits the targeting construct of claim 1 to comprising a screening marker gene and claims 3 and 4 are directed to a method of making the targeting construct having the features of the targeting construct of claim 1.

As described in the previous Office Action, Qin *et al.* teach a nucleic acid molecule comprising a nucleic acid sequence homologous to a cGMP phosphodiesterase alpha subunit gene. Qin *et al.* does not teach that the sequence should be configured as a targeting vector

comprising a selectable marker gene located between the first and second polynucleotide sequences.

Tsang *et al.* teaches construction of a targeting vector having the structural characteristics of the targeting vector of the instant claims 1 and 2, except for the inclusion of a cGMP phosphodiesterase alpha subunit gene (see especially Figure 1A and the caption thereto), for the purpose of generating a transgenic mouse comprising a homologous disruption of the cGMP phosphodiesterase gamma subunit gene. Tsang further teaches a method of constructing a targeting vector according to the instant claims 3 and 4 (see endnote 18). Tsang *et al.* teaches that mice constructed in this way are useful to study their role of the cGMP phosphodiesterase subunit in retinal degeneration (paragraph bridging the middle and right columns on page 1026).

Dryja *et al.* teaches that mutations in the rod cGMP phosphodiesterase alpha subunit gene are linked to retinitis pigmentosa in humans.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct a targeting vector according to the teachings of Tsang *et al.* using the nucleic acid encoding a cGMP phosphodiesterase gene according to the teachings of Qin *et al.* to produce the targeting vector of the instant claims 1 and 2 by the method of claims 3 and 4.

One would be motivated to combine these teachings in view of the teachings of Dryja *et al.* and Tsang *et al.* Dryja *et al.* teaches that cGMP phosphodiesterase alpha gene disruptions correlate with retinitis pigmentosa in humans, and Tsang *et al.* teaches that disruption of cGMP phosphodiesterase subunits in mice results in retinal degeneration analogous to retinitis pigmentosa. In view of these teachings, the skilled artisan would be motivated to make the targeting constructs in order to investigate the role of the cGMP phosphodiesterase α subunit

gene in retinitis pigmentosa. Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because construction of targeting constructs is routine in the art.

For these reasons, the invention of claims 1-4, as a whole, would have been obvious to one of ordinary skill in the art at the time of filing and the claims are properly rejected under 35 USC §103.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER